DETAILED ACTION

Receipt is acknowledged of applicant's Amendment/Remarks filed 1/14/2010. Claims 1-2, 7, and 10-19 were previously cancelled. Claims 26-30 remain withdrawn as pertaining to the non-elected invention. Claims 3-6, 8-9, and 20-30 are pending. Claims 3-6, 8-9, and 20-25 are currently under consideration.

MAINTAINED REJECTIONS

1. The following rejections have been maintained from the previous Office Action dated 1/14/2010:

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 3-6, 8-9, and 20-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dahlström et al. ("Relation Between Morphine Pharmokinetics and Analgesia," *Journal of Pharmokinetics and Biopharmaceutics*, Vol. 6, No. 1, 1978, pgs 41-53) in view of Inturrisi (6,00,258).

The instant claims 3-9 and 20-23 are directed to methods of providing analgesia comprising administering a pharmaceutical composition(s) comprising enantiomerically pure L-methadone or a mixture of DL methadone having at least 65% L-methadone, and morphine, wherein the pharmaceutical composition(s) is/are administered in an amount and duration sufficient to potentiate an antinociceptive response. Claims 24-25 are directed to methods of potentiating an antinociceptive response comprising administering a pharmaceutical composition(s) comprising enantiomerically pure L-methadone or a mixture of DL methadone having at least 65% L-methadone, and morphine, wherein the pharmaceutical composition(s) is/are administered in an amount and duration sufficient to potentiate an antinociceptive response.

In regards to the recitation in claims 3-4 of "wherein the pharmaceutical composition(s) is/are administered in an amount and duration sufficient to potentiate an antinociceptive response," the amounts and duration sufficient to obtain this effect is not defined in the specification. Therefore, claims 3-4 and 22-25 (all containing similar recitations) are broadly interpreted as administering any amount of L-methadone and morphine in any manner or duration.

Dahlström et al. teach administering morphine to male Sprague-Dawley rats at four different dosages (1.7, 2.5, 3.8, and 5.6 mg/kg) to elicit an analgesic effect (see pages 42-43). The analgesic effect is dose-dependent (see page 44, Figures 1-2).

Dahlström et al. do not teach administering enantiomerically pure L-methadone or a mixture of DL methadone having at least 65% L-methadone, or the dosage of L-methadone as claimed in the instant claims 5-6. Dahlström et al. do not explicitly teach the dosage of morphine in mg as claimed in the instant claims 8-9.

Inturrisi teaches in an exemplary test that L-methadone produces dose-dependent antinociception (analgesia) in rats with an ED_{50} value of 15.6 μg/rat, while D-methadone produced no antinociceptive effects at doses from 20 to 460 μg/rat (see column 3, lines 51-57). Inturrisi teaches that the D-isomer of methadone is 50-fold less potent analgesic in humans than L-methadone (see column 3, lines 27-33).

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat analgesia by administering a combination of the morphine taught by Dahlström et al. and the L-isomer of methadone taught by Inturrisi. One of ordinary skill in the art would have been motivated to treat analgesia by combining morphine and L-methadone because both agents are taught in the prior art to have an analgesic effect. Further, one of ordinary skill in the art would have been motivated to use the L-isomer of methadone, or an increased amount of the L-isomer of methadone, in the method of treating analgesia because L-methadone is taught by Inturrisi to be the active isomer for providing an analgesic effect, whereas the D-isomer is relatively inactive. One of ordinary skill in the art would have had a reasonable expectation of success in treating

analgesia by combining the morphine taught by Dahlström et al. and the L-isomer of methadone taught by Inturrisi because both agents are taught by the prior art to provide an analgesic effect. It is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose *In re Kerkhoven*, 626 F.2d 846, 205, U.S.P.Q. 1069 (C.C.P.A. 1980). Thus, combining the morphine taught by Dahlström et al. and the L-isomer of methadone taught by Inturrisi to provide a composition for providing an analgesic effect is obvious because both agents are taught by the prior art to provide an analgesic effect.

While the prior art references do not explicitly teach the dosage range of L-methadone or morphine in mg as claimed in the instant claims 5-6 and 8-9, the determination of an optimal dosage of L-methadone and morphine by routine experimentation is obvious absence a showing of criticality of the dosage. One have ordinary skill in the art would have been motivated to optimize the dosage of L-methadone and morphine in order to achieve the desired analgesic effects.

In regards to claims 24-25, the ability of compositions comprising enantiomerically pure L-methadone or a mixture of DL methadone having at least 65% L-methadone and morphine to potentiate an antinociceptive response is viewed as a mechanism of action. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. *In re Wiseman*, 201 USPQ 658 (CCPA 1979). Since the method of providing analgesia obvious over Dahlström et al. in view of Inturrisi involves

administering the same active agents to the same patient population at the same dosage, the method of providing analgesia will obviously potentiate an antinociceptive response.

Response to Amendment

4. The declaration under 37 CFR 1.132 filed 1/14/2010 is insufficient to overcome the rejection of claims 3-6, 8-9, and 20-25 under 35 U.S.C. 103(a) as being unpatentable over Dahlström et al. ("Relation Between Morphine Pharmokinetics and Analgesia," *Journal of Pharmokinetics and Biopharmaceutics*, Vol. 6, No. 1, 1978, pgs 41-53) in view of Inturrisi (US 6,00,258) as set forth in the last Office action because: sufficient scientific and/or factual evidence has not been presented to rebut the *prima facie* case of obviousness made in the 103(a) rejection. The declaration submitted expresses an opinion and does not provide any factually supported objective evidence. In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Response to Arguments

5. Applicant's arguments filed 1/14/2010 have been fully considered but they are not persuasive.

The Applicant argues that *In re Kerkhoven* does not apply to the treatment of pain, and that prior to the present invention, the common strategy of one of ordinary skill in the art of combination therapy was to utilize two or more drugs of different

mechanisms so as to reduce potential side effects. In response it is respectfully submitted that regardless of the mechanism of action of the agents, it has been well established that it is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose *In re Kerkhoven*, 626 F.2d 846, 205, U.S.P.Q. 1069 (C.C.P.A. 1980). It is also noted that while *In re Kerkhoven* is not directed to the combination of compositions for the treatment of pain, there is nothing precluding the standard established by *In re Kerkhoven* from applying to compositions for the treatment of pain. Furthermore, it is not guaranteed that an increase in side effects will be observed in combining two agents acting via the same mechanism.

The Applicant further argues that one of ordinary skill in the art would not have been motivated to use a combination of two opioid analgesic agents to effect analgesia because as submitted in the Declaration filed 1/14/2010, Dr. Inturrisi states that "prior to the Application, it was believed that use of two opioid analgesic agents would have little added benefit as the two agents would compete for the same receptors and would thus be no more effective than using one agent at full dosage." In response it is respectfully submitted that the arguments of counsel cannot take the place of evidence in the record. *In re Schulz*, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 43 USPQ2d 1362 (Fed. Circ. 1997) (“An assertion of what seems to follow from common experience is just an attorney argument and is not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness.") As stated *supra*, the opinion expressed in the declaration is not factually supported objective evidence needed to rebut a *prima*

facie case of obviousness. In addition, it is noted that the instant claims 3-4 and 20-25 do not claim dosage ranges, and the instant claims 5-6 and 8-9 claim broad dosage ranges for one opioid analgesic at a time. Thus, as instantly claimed, the opioid analgesics are not necessarily administered at sufficient dosage ranges to saturate the receptors. Moreover, it is unclear as to what dosages of morphine or L-methadone would be required to saturate the receptors since when dosage ranges are claimed, such a broad ranges is claimed that is unlikely that the receptors are saturated throughout that entire range. Thus, the combination of L-methadone and morphine is still deemed to be obvious.

The Applicant further argues that that combination of methadone and morphine in Smith et al. did not result in even an additive effect from the combination; but in fact had a less than desirable effect that using morphine alone. In response it is respectfully submitted that Smith teaches administration of methadone and morphine at one specific dosage combination and utilizes racemic methadone instead of the enantiomerically enriched or enantiomerically pure L-methadone. Moreover, Smith et al. teach that some combinations of opioid analgesic agents do produce additive effects. For example, Smith et al. teach additive analgesic effects were obtained with combinations of methadone and alpha-acetylmethadol and alpha-acetylmethadol levorotatory.

Thus, for these reasons, Applicant's arguments are found unpersuasive. Said rejection is maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jody L. Karol whose telephone number is (571)270-3283. The examiner can normally be reached on 8:30 am - 5:00 pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Jody L. Karol/

Examiner, Art Unit 1627

/Yong S. Chong/
Primary Examiner, Art Unit 1627